treatment of the brain by intracranial administration, which means that a hole must be made in the skull and that the treatment of IGF is conducted through the hole in the skull. As previously noted by applicant (see Amendment and Remarks filed April 10, 1999), Lewis teaches away from parenteral nonintracranial administration of a nonmodified IGF by asserting that a naturally-occurring IGF does not cross the blood-brain barrier:

> Where the polypeptide is intended for use as a therapeutic for disorders of the CNS, an additional problem must be addressed: overcoming the so-called "blood-brain barrier," the brain capillary wall structure that effectively screens out all but selected categories of molecules present in the blood, preventing their passage into the brain. While the blood-brain barrier may be effectively bypassed by direct infusion of the polypeptide into the brain, the search for a more practical method has focused on enhancing transport of the polypeptide of interest across the blood-brain barrier, such as by making the polypeptide more lipophilic, by conjugating the polypeptide of interest to a molecule which is naturally transported across the barrier, or by reducing the overall length of the polypeptide chain.

Lewis et al., col. 3, lines 44-58.

Even the Examples of Lewis are limited to either *in vitro* experiments or administration of modified IGF to rat models via a hole in the skull: **1)** *in vitro* methods for measuring effectiveness of IGF treatment (Examples 1-3); **2)** administration of IGF by intracerebral injection (*i.e.*, injection through a hole in the skull) (Examples 4 and 5); **3)** methods for modifying IGF's (Examples 6-10); and **4)** an *in vitro* method for measuring the effectiveness of the IGF modifications (Example 11). Nowhere does Lewis et al. teach or even suggest the administration of IGF's via a parenteral nonintracranial method. On the contrary, Lewis et al. emphatically and unmistakably teach that the IGF must either be modified or be delivered intracranially. Therefore, Lewis et al. does not teach or suggest a method of administering IGFs that is both parenteral and nonintracranial.

The Examiner also asserts that "[applicant's] claimed limitation directed to IGF is the same scope as the IGF claimed which includes functional derivatives and unmodified IGF." (Office Action mailed December 8, 1999, p. 2.) That statement is not correct, as the scope of the IGF in applicant's claims does not include the "functional derivatives" of Lewis et al. Lewis et al. alleges that diseases such as Alzheimer's and Parkinson's are therapeutically "administering to the animal an effective amount of a functional derivative, e.g. a fragment or analog of IGF-I or of IGF-II" (column 4, lines 3-5; emphasis added). A method for enhancing the cholinergic activity of cholinergic neuronal cells is alleged to be accomplished by "administering to the mammal an effective amount of a functional derivative of IGF-I or IGF-II, preferably a fragment of IGF-I, of IGF-II or, alternatively, an analog of IGF-I , of IGF-II, or of a fragment of IGF-I or IGF-II" (column 4, lines 16-20; emphasis added). Furthermore, Lewis et al recite that "[t]he method of the invention uses functional derivatives of IGF-I and of IGF-II to enhance the survival rate and/or the cholinergic activity of mammalian cells at an increased risk of death due to some factor such as disease, injury, or natural aging process" (column 4, lines 31-35; emphasis added). Finally, Lewis et al. specifically teach that their "invention is directed to the modification of neuroactive polypeptides such as IGF-I and IGF-II and their functional derivatives" (column 5, lines 60-62; emphasis added).

To clarify the distinction, claims 24, 29, 34, 37, 40, 43, 46 and 57 are amended above to indicate that applicant's invention involves an IGF that "consists essentially of an amino acid sequence of a naturally occurring IGF."

Therefore, the rejection under 35 U.S.C. § 102(b) based on Lewis et al. should be withdrawn.

* * *

The Examiner is invited to contact the undersigned attorney at (713) 787-1686 with any questions comments relating to this patent application.

Should any other fee be required for any reason in connection with this Response, the Assistant Commissioner is authorized to deduct said fees from Howrey Simon Arnold & White Deposit Account No. 01-2508/CSUA019--1/WAA.

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